# INTERNATIONAL SEARCH REPORT

International application No.
PCT/US04/22594

A. CLASSIFICATION OF SUBJECT MATTER
IPC: **C07H 19/00**( 2006.01),**21/02**( 2006.01),**21/04**( 2006.01)

USPC: 536/22.1,24.3,24.31
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
U.S. : 536/22.1, 24.3, 24.31

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
Please See Continuation Sheet

C. DOCUMENTS CONSIDERED TO BE RELEVANT

| Category * | Citation of document, with indication, where appropriate, of the relevant passages | Relevant to claim No. |
|---|---|---|
| Y | US 2002/0090624 A1 (BLUMENBERG) 11 July 2002 (11.07.2002), see the entire document, especially tables 2 and 5. | 1-4,7-9,49 |
| Y | Database, Entrez Nucleotide Database Entry for XM_051900, 27 August 2001, see entire document. | 1-4,7-9,49 |
| Y | Database, Entrez Nucleotide Database Entry for XM_031289, 27 August 2001, see entire document. | 1-4,7-9,49 |

☐ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier application or patent published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search
09 May 2008 (09.05.2008)

Date of mailing of the international search report
30 MAY 2008

Name and mailing address of the ISA/US
Mail Stop PCT, Attn: ISA/US
Commissioner for Patents
P.O. Box 1450
Alexandria, Virginia 22313-1450
Facsimile No. (571) 273-3201

Authorized officer
Daniel M. Sullivan

Telephone No. 703-308-0196

Form PCT/ISA/210 (second sheet) (April 2007)

# INTERNATIONAL SEARCH REPORT

International application No.
PCT/US04/22594

**Box No. I Nucleotide and/or amino acid sequence(s) (Continuation of item 1.c of the first sheet)**

1. With regard to any nucleotide and/or amino acid sequence disclosed in the international application, the international search was carried out on the basis of:

   a. type of material

   ☒ a sequence listing

   ☒ table(s) related to the sequence listing

   b. format of material

   ☒ on paper

   ☒ in electronic form

   c. time of filing/furnishing

   ☒ contained in the international application as filed

   ☒ filed together with the international application in electronic form

   ☐ furnished subsequently to this Authority for the purposes of search

2. ☐ In addition, in the case that more than one version or copy of a sequence listing and/or table relating thereto has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that in the application as filed or does not go beyond the application as filed, as appropriate, were furnished.

3. Additional comments:

# INTERNATIONAL SEARCH REPORT

International application No.
PCT/US04/22594

**Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)**

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

**Box No. III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)**

This International Searching Authority found multiple inventions in this international application, as follows:
Please See Continuation Sheet

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying additional fees, this Authority did not invite payment of any additional fees.
3. ☒ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.: 1-4,7-9 and 49

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

**Remark on Protest**

☐ The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.

☐ The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.

☒ No protest accompanied the payment of additional search fees.

BOX III. OBSERVATIONS WHERE UNITY OF INVENTION IS LACKING

This application contains the following inventions or groups of inventions which are not so linked as to form a single general inventive concept under PCT Rule 13.1. In order for all inventions to be examined, the appropriate additional examination fees must be paid.

This application contains the following inventions or groups of inventions which are not so linked as to form a single inventive concept under PCT Rule 13.1 In order for all inventions to be searched, the appropriate additional search fees must be paid.

Group 1, claims 1-4, 7-9, 49, all-in-part, drawn to a panel of biomarkers comprising SEQ ID NOS 1 and 2 and a method for measuring the level of SEQ ID NOS 1 and 2.

Group 2, claims 1-4, 7-9, 49, all-in-part, drawn to a panel of biomarkers comprising at least two of SEQ ID Nos 1-5, other than a panel comprising SEQ ID NOS 1 and 2 alone, wherein each combination of sequences to be searched must be identified and additional fees must be paid for each combination of sequences searched.

Group 3, claims 10-13, 16-18, all-in-part, drawn to a panel of biomarkers comprising at least two of SEQ ID Nos 1-5 and at least one of SEQ ID NOS 6-14, wherein each combination of sequences to be searched must be identified and additional fees must be paid for each combination of sequences searched.

Group 4, claims 19-22, 25-27, all-in-part, drawn to a panel of biomarkers comprising at least two of SEQ ID Nos 1-5 and at least one of SEQ ID NOS 6-14 and at least one of SEQ ID NOS 15-22, wherein each combination of sequences to be searched must be identified and additional fees must be paid for each combination of sequences searched.

Group 5, claims 28-29, 32-34, all-in-part, drawn to a panel of biomarkers comprising at least two of SEQ ID Nos 23-27, wherein each combination of sequences to be searched must be identified and additional fees must be paid for each combination of sequences searched.

Group 6, claims 35-36, 39-41, all-in-part, drawn to a panel of biomarkers comprising at least two of SEQ ID Nos 23-27 and at least one of SEQ ID NOS 28-36, wherein each combination of sequences to be searched must be identified and additional fees must be paid for each combination of sequences searched.

Group 7, claims 42-43, 46-48, all-in-part, drawn to a panel of biomarkers comprising at least two of SEQ ID Nos 23-27 and at least one of SEQ ID NOS 28-36 and at least one of SEQ ID NOS 37-44, wherein each combination of sequences to be searched must be identified and additional fees must be paid for each combination of sequences searched.

Group 8, claims 49, 53-64, all-in-part, 52-in-part as it is drawn to the searched invention, drawn to a method for measuring expression levels of polynucleotide biomarkers comprising selecting at least two polynucleotides from SEQ ID NOS 1-5, other than SEQ ID NOS 1 and 2 alone, isolating cellular RNA from the sample, amplifying cDNA and quantifying levels of amplified cDNA, wherein each combination of sequences to be searched must be identified and additional fees must be paid for each combination of sequences searched.

Group 9, claims 49, 50, 51, 53-64, all-in-part, 52-in-part as it is drawn to the searched invention, drawn to a method for measuring expression levels of polynucleotide biomarkers comprising selecting at least two polynucleotides from SEQ ID NOS 1-5 and at least one polynucleotide from SEQ ID NOS 6-14 and at least one polynucleotide from SEQ ID NOS 15-22, isolating cellular RNA from the sample,

amplifying cDNA and quantifying levels of amplified cDNA, wherein each combination of sequences to be searched must be identified and additional fees must be paid for each combination of sequences searched.

Group 10, claims 65, 68-78, all-in-part, drawn to a method for measuring expression levels of polypeptide biomarkers comprising selecting at least two polypeptides from SEQ ID NOS 23-27, creating an antibody panel for each biomarker in the panel, binding antibody to polypeptides and quantifying levels of polypeptides bound from the sample to the antibody panel, wherein each combination of sequences to be searched must be identified and additional fees must be paid for each combination of sequences searched.

Group 11, claims 65, 66, 68-78, all-in-part, drawn to a method for measuring expression levels of polypeptide biomarkers comprising selecting at least two polypeptides from SEQ ID NOS 23-27 and at least one polypeptide from SEQ ID NOS 28-36, creating an antibody panel for each biomarker in the panel, binding antibody to polypeptides and quantifying levels of polypeptides bound from the sample to the antibody panel wherein each combination of sequences to be searched must be identified and additional fees must be paid for each combination of sequences searched.

Group 12, claims 65-78, all-in-part, drawn to a method for measuring expression levels of polypeptide biomarkers comprising selecting at least two polypeptides from SEQ ID NOS 23-27 and at least one polypeptide from SEQ ID NOS 28-36 and at least one polypeptide from SEQ ID NOS 27-44, creating an antibody panel for each biomarker in the panel, binding antibody to polypeptides and quantifying levels of polypeptides bound from the sample to the antibody panel wherein each combination of sequences to be searched must be identified and additional fees must be paid for each combination of sequences searched.

Group 13, claims 79-83, 84-in-part, 85-88 drawn to a kit for the determination of colorectal cancer and colorectal polyps comprising at least one reagent that is used in analysis of polynucleotide expression levels comprising at least two sets of primers chosen from SEQ ID NOS 45-50 and instructions for using the kit wherein each combination of sequences to be searched must be identified and additional fees must be paid for each combination of sequences searched.

Group 14, claims 89, 92-95 drawn to a kit for the determination of colorectal cancer and colorectal polyps comprising at least one reagent that is used in analysis of polypeptide expression levels comprising an antibody that binds to a polypeptide and instructions for using the kit.

The inventions listed as Groups 1-14 do not relate to a single general inventive concept under PCT Rule 13.1 because, under PCT Rule 13.2, they lack the same or corresponding special technical features for the following reasons:

An international stage application shall relate to one invention only or to a group of inventions so linked as to form a single general inventive concept. When claims to different categories are present in the application, the claims will be considered to have unity of invention if the claims are drawn only to one of the following combinations of categories: (1) A product and a process specially adapted for the manufacture of said product; or (2) A product and a process of use of said product; or (3) A product, a process specially adapted for the manufacture of the said product, and a use of the said product; or (4) A process and an apparatus or means specifically designed for carrying out the said process; or (5) A product, a process specially adapted for the manufacture of the said product, and an apparatus or means specifically designed for carrying out the said process. If multiple products, processes of manufacture or uses are claimed, the first invention of the category first mentioned in the claims of the application will be considered as the main invention in the claims, see PCT article 17(3) (a) and 1.476 (c), 37 C.F.R. 1.475(b) and (d). Group I will be the main invention. After that, all other products and methods will be broken out as separate groups (see 37 CFR 1.475(d).)

Group 1 forms a single general inventive concept, that is a panel of biomarkers comprising SEQ ID NOS 1 and 2 and a method for measuring the level of SEQ ID NOS 1 and 2.

Groups 2-14 do not have unity of invention with Group 1 because they are inventions drawn to methods and products that are different than the first invention claimed.

Group 1 is the main invention. After that, all other methods and products not used in that invention have been properly broken out as separate groups (see 37 CFR 1.475(d).) because they are not drawn to the permitted combinations of categories for unity of invention.

Accordingly, Groups 1-14 are not so linked as to form a single general inventive concept.

## INTERNATIONAL SEARCH REPORT

International application No.
PCT/US04/22594

Continuation of B. FIELDS SEARCHED Item 3:
EAST (USPAT, USPGPUB, EPO, JPO, DERWENT), STN (medline, caplus). Search terms: Interleukin 8, prostaglandin-endoperoxide synthase 2, Interleukin 8 receptor B, lipocalin 2, Serum amyloid A1

# PATENT COOPERATION TREATY

From the
INTERNATIONAL SEARCHING AUTHORITY

To:
HELLER EHRMAN LLP
4350 LA JOLLA VILLAGE DRIVE
SAN DIEGO, CA 92122-1246

# PCT

## WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

(PCT Rule 43*bis*.1)

| | |
|---|---|
| Date of mailing (*day/month/year*) | 30 MAY 2008 |
| Applicant's or agent's file reference<br>26837-2-1PC | **FOR FURTHER ACTION**<br>See paragraph 2 below |

| International application No. | International filing date (*day/month/year*) | Priority date (*day/month/year*) |
|---|---|---|
| PCT/US04/22594 | 14 July 2004 (14.07.2004) | 18 July 2003 (18.07.2003) |

International Patent Classification (IPC) or both national classification and IPC

IPC: **C07H 19/00**( 2006.01),**21/02**( 2006.01),**21/04**( 2006.01)
USPC: 536/22.1,24.3,24.31

Applicant

NANCY M. LEE

1. This opinion contains indications relating to the following items:

- ☒ Box No. I — Basis of the opinion
- ☐ Box No. II — Priority
- ☐ Box No. III — Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- ☒ Box No. IV — Lack of unity of invention
- ☒ Box No. V — Reasoned statement under Rule 43*bis*.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- ☐ Box No. VI — Certain documents cited
- ☐ Box No. VII — Certain defects in the international application
- ☐ Box No. VIII — Certain observations on the international application

2. **FURTHER ACTION**

If a demand for international preliminary examination is made, this opinion will be considered to be a written opinion of the International Preliminary Examining Authority ("IPEA") except that this does not apply where the applicant chooses an Authority other than this one to be the IPEA and the chosen IPEA has notified the International Bureau under Rule 66.1*bis*(*b*) that written opinions of this International Searching Authority will not be so considered.

If this opinion is, as provided above, considered to be a written opinion of the IPEA, the applicant is invited to submit to the IPEA a written reply together, where appropriate, with amendments, before the expiration of 3 months from the date of mailing of Form PCT/ISA/220 or before the expiration of 22 months from the priority date, whichever expires later.

For further options, see Form PCT/ISA/220.

3. For further details, see notes to Form PCT/ISA/220.

| Name and mailing address of the ISA/ US | Date of completion of this opinion | Authorized officer |
|---|---|---|
| Mail Stop PCT, Attn: ISA/US<br>Commissioner for Patents<br>P.O. Box 1450<br>Alexandria, Virginia 22313-1450<br>Facsimile No. (571) 273-3201 | 09 May 2008 (09.05.2008) | Daniel M. Sullivan<br>Telephone No. 703-308-0196 |

Form PCT/ISA/237 (cover sheet) (April 2007)

**WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY**

International application No.
PCT/US04/22594

**Box No. I Basis of this opinion**

1. With regard to the **language**, this opinion has been established on the basis of:

☒ the international application in the language in which it was filed

☐ a translation of the international application into _____, which is the language of a translation furnished for the purposes of international search (Rules 12.3(a) and 23.1(b)).

2. ☐ This opinion has been established taking into account the **rectification of an obvious mistake** authorized by or notified to this Authority under Rule 91 (Rule 43*bis*.1(a))

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, this opinion has been established on the basis of:

a. type of material

☒ a sequence listing

☒ table(s) related to the sequence listing

b. format of material

☒ on paper

☒ in electronic form

c. time of filing/furnishing

☒ contained in the international application as filed.

☒ filed together with the international application in electronic form.

☐ furnished subsequently to this Authority for the purposes of search.

4. ☐ In addition, in the case that more than one version or copy of a sequence listing and/or table(s) relating thereto has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that in the application as filed or does not go beyond the application as filed, as appropriate, were furnished.

5. Additional comments:

**WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY**

International application No.
PCT/US04/22594

**Box No. IV Lack of unity of invention**

1. ☒ In response to the invitation (Form PCT/ISA/206) to pay additional fees the applicant has, within the applicable time limit:
   - ☒ paid additional fees
   - ☐ paid additional fees under protest and, where applicable, the protest fee
   - ☐ paid additional fees under protest but the applicable protest fee was not paid
   - ☐ not paid additional fees
2. ☐ This Authority found that the requirement of unity of invention is not complied with and chose not to invite the applicant to pay additional fees.
3. This Authority considers that the requirement of unity of invention in accordance with Rule 13.1, 13.2 and 13.3 is
   - ☐ complied with
   - ☒ not complied with for the following reasons:

   See the lack of unity section of the International Search Report(Form PCT/ISA/210)

4. Consequently, this opinion has been established in respect of the following parts of the international application:
   - ☐ all parts.
   - ☒ the parts relating to claims Nos. 1-4,7-9 and 49

**WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY**

International application No.
PCT/US04/22594

**Box No. V Reasoned statement under Rule 43 *bis*.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement**

1. Statement

| | | |
|---|---|---|
| Novelty (N) | Claims 1-4,7-9,49 | YES |
| | Claims NONE | NO |
| Inventive step (IS) | Claims NONE | YES |
| | Claims 1-4,7-9,49 | NO |
| Industrial applicability (IA) | Claims 1-4,7-9,49 | YES |
| | Claims NONE | NO |

2. Citations and explanations:

Claims 1-4, 7-9 and 49 lack an inventive step under PCT Article 33(3) as being obvious over Blumenberg US Pub. No. 2002/0090624 A1 in view of Entrez Nucleotide database entries for XM_031289 (2002) and XM_051900 (2001).

Blumenberg describes a panel of biomarkers including IL-8 (Table 5) and PTGS2 (Table 2) and teaches methods of using the panel to measure expression of the genes in patient samples. Although Blumberg does not specify the sequences of SEQ ID NO: 1 or 2 recited in the instant claims, those sequences were known in the art at the time the invention was filed (See Entrez Nucleotide database entries for XM_031289 and XM_051900) and, therefore, using those sequences in a panel of biomarkers does not represent an inventive step with respect to the prior art. In addition, although some claims recite an intended use for the panel of biomarkers and method which is not disclosed in the prior art, the intended use does not impart any patentable distinction on the panel itself and therefore does not distinguish the claims from the prior at.

Claims 1-4, 7-9 and 49 meet the criteria set out in PCT Article 33(4), and thus have industrial applicability because the subject matter claimed can be made or used in industry.